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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/SE98/00038</p> <p>(22) International Filing Date: 13 January 1998 (13.01.98)</p> <p>(30) Priority Data: 9700133-3 20 January 1997 (20.01.97) SE</p> <p>(71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).</p> <p>(72) Inventor; and (75) Inventor/Applicant (for US only): TROFAST, Jan [SE/SE]; Vapenkroken 34, S-226 47 Lund (SE).</p> <p>(74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: NEW FORMULATION FOR INHALATION HAVING A POURED BULK DENSITY OF FROM 0.28 TO 0.38 G/ML, COMPRISING BUDESONIDE</p> <p>(57) Abstract</p> <p>A dry powder composition comprising budesonide and a carrier substance, both of which are in finely divided form, wherein the formulation has a poured bulk density of from 0.28 to 0.38 g/ml is useful in the treatment of respiratory disorders.</p>		

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NEW FORMULATION FOR INHALATION HAVING A POURED BULK DENSITY OF FROM 0.28 TO 0.38 G/ML,  
COMPRISING BUDESONIDE

*Field of the Invention*

The present invention provides a new pharmaceutical formulation, its preparation and its  
5 use.

*Background to the Invention*

Potent drugs for administration by inhalation are generally formulated in association with  
carriers such as lactose because of the problem of preparing accurate doses. When such  
10 drugs are diluted, variations in the weight of the formulation result in a smaller drug dosage  
variation rate compared with when they are not diluted. These formulations have generally  
consisted of coarse particles of the carrier with fine particles of the drug, which  
combination is generally known as an ordered mixture.

15 The invention provides an improved formulation which, in systems designed to imitate  
inhalation has been found to give an improved dispersion of the drug.

*Description of the Invention*

According to the invention there is provided a dry powder composition comprising  
20 budesonide and a carrier substance, both of which are in finely divided form, wherein the  
formulation has a poured bulk density of from 0.28 to 0.38 g/ml, preferably from 0.30 to  
0.36 g/ml.

The poured bulk density according to the present invention is measured using known  
25 techniques, for example those described in "Powder testing guide: Methods of measuring  
the physical properties of Bulk powders" L. Svarovsky, Elsevier Applied Science 1987, pp  
84-86.

The carrier substance is preferably a mono-, di- or polysaccharide, a sugar alcohol or another polyol. Suitable carriers are, for example, lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol; and starch. Lactose is particularly preferred, especially in the form of its monohydrate.

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The ingredients of the formulation according to the invention must both be in a finely divided form, i.e. their mass median diameter should generally be less than 10  $\mu\text{m}$ , preferably from 1 to 7  $\mu\text{m}$ , as measured by a laser diffraction instrument or a coulter counter. The ingredients may be produced in the desired particle size using methods  
10 known to those of skill in the art, e.g. milling, micronisation or direct precipitation.

The composition according to the invention is preferably formulated to comprise, as a daily dose, from 20 to 4300  $\mu\text{g}$  of budesonide (preferably from 80 to 2150  $\mu\text{g}$ ). More preferably the composition is formulated to provide unit doses of 200  $\mu\text{g}$  or 400  $\mu\text{g}$  of budesonide.

15 The composition is preferably formulated to comprise in each unit dose from 50  $\mu\text{g}$  to 25 mg of the carrier substance, more preferably from 50  $\mu\text{g}$  to 10mg, most preferably from 100 to 4000  $\mu\text{g}$ .

According to the invention there is further provided a process for preparing a composition  
20 according to the invention which comprises

- (a) micronising budesonide and the carrier substance;
- (b) optionally conditioning the product; and
- (c) spheronizing until the desired bulk density is obtained.

The process preferably further comprises a low energy remicronisation step after step (b).

25

The formulation according to the invention may be made by conventional techniques known *per se*. Such production processes generally comprise micronising the ingredients to the required size, removing any amorphous areas on the particles obtained by, for example, the methods described in WO 92/18110 or WO 95/05805 and then  
30 agglomerating, spheronising and sieving the powder obtained. The size of the

agglomerates obtained is preferably in the range of from 100 to 2000  $\mu\text{m}$ , more preferably from 100 to 800  $\mu\text{m}$ . The bulk density of the formulation produced may be adjusted by varying the components and the process empirically, for example the bulk density can be increased by lengthening the time in which the particles are tumbled in a spheronising  
5 device.

In solid-solid mixing, one of the most important features is to ensure content uniformity. The major problem encountered in the powder mixing of fine powders is the inability of mixers to break down powder agglomerates. It has been found that a remicronisation step  
10 after the conditioning step of the fine powder with low energy input is advantageous. It should generally be carried out using enough energy to break down powder agglomerates but not with so much energy that the size of the particles themselves is affected. Such a step gives a composition wherein the active substance and carrier substance are substantially uniformly distributed, having for example a relative standard deviation of less  
15 than 3% (preferably less than 1%) without disturbing the crystallinity of the fine particles.

The formulation according to the invention may be administered using any known dry powder inhaler, for example the inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler, for example Turbuhaler (trade mark). The invention  
20 further provides use of a composition according to the invention in the manufacture of a medicament for use in therapy. The composition according to the invention is useful in the treatment of respiratory disorders, particularly asthma. The invention also provides a method of treating a patient suffering from a respiratory disorder which comprises administering to the patient a therapeutically effective amount of a composition according  
25 to the invention.

The invention is illustrated, but not limited, by reference to the following Example.

*Example*

9 Parts of budesonide and 91 parts of lactose monohydrate were micronised separately in a spiral jet mill at a pressure of about 6-7 bars to give a particle size of less than 3  $\mu\text{m}$  before being mixed thoroughly in a Turbula mixer. Before mixing, the lactose monohydrate powder was conditioned according to the method described in WO 95/05805. The mixture was remicronised in a spiral jet mill at a pressure of only about 1 bar to obtain a uniform mixture. The powder was then agglomerated by feeding the powder into a twin screw feeder (K-Tron), sieving in an oscillating sieve (0.5 mm mesh size), spheronising in a rotating pan with a peripheral speed of 0.5m/s for 4 minutes and then sieving again using the same sieve, then spheronising once more for 6 minutes before final sieving (mesh size 1.0 mm) giving a powder with a bulk density of 0.35 g/ml.

*Claims*

1. A dry powder composition comprising budesonide and a carrier substance, both of which are in finely divided form, wherein the formulation has a poured bulk density of  
5 from 0.28 to 0.38 g/ml.
2. A composition according to claim 1 wherein the bulk density is from 0.30 to 0.36 g/ml.
- 10 3. A composition according to claim 1 or 2 wherein the active substance and carrier substance are substantially uniformly distributed.
4. A composition according to claim 1, 2 or 3 for use in the treatment of a respiratory disorder.
- 15 5. A process for preparing a composition according to claim 1 which comprises
  - (a) micronising budesonide and the carrier substance;
  - (b) optionally conditioning the product; and
  - (c) spheronizing until the desired bulk density is obtained.
- 20 6. A process according to claim 5 which comprises a low energy remicronisation step after step (b).
7. Use of a composition according to claim 1, 2 or 3 in the manufacture of a medicament  
25 for use in therapy.
8. A method of treating a patient suffering from a respiratory disorder which comprises administering to the patient a therapeutically effective amount of a composition according to claim 1, 2 or 3.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/00038

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
IPC6: A61K 9/72, A61K 31/58 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols)		
IPC6: A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
SE,DK,FI,NO classes as above		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
WPI, USPATFULL, CAPLUS		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5551489 A (EVA A. C. TROFAST ET AL), 3 Sept 1996 (03.09.96), column 2, line 8 - line 15  --	1-8
X	US 4590206 A (RAYMOND B. FORRESTER ET AL), 20 May 1986 (20.05.86), column 4, line 15 - line 21; column 4, line 42 - line 53  -- -----	1-8
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
13 May 1998		19 -05- 1998
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# INTERNATIONAL SEARCH REPORT

Inter. application No.

PCT/SE 98/00038

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 8  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Claim 8 is directed to method of treatment of the human or animal body by therapy methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claims. The search has been based on the alleged effects of the composition.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

29/04/98

International application No.  
PCT/SE 98/00038

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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